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Cytotoxic chemotherapy

Patients whose tumors have progressed on hormone therapy are candidates for cytotoxic chemotherapy. Patients with hormone receptor-negative tumors and those with visceral metastases are also candidates for cytotoxic agents.

Single agents that have shown activity in metastatic breast cancer:

- · Anthracyclines.
 - Doxorubicin.
 - Epirubicin.
 - Liposomal doxorubicin.[50-52]
 - Mitoxantrone.
- Taxanes.
 - Paclitaxel.
 - Docetaxel.
 - Albumin-bound nanoparticle paclitaxel (ABI-007 or Abraxane).[53]
- · Alkylating agents.
 - Cyclophosphamide.
- Fluoropyrimidines.
 - Capecitabine.[54,55]
 - 5-FÙ.
- Antimetabolites.
 - Methotrexate.
- · Vinca alkaloids.
 - Vinorelbine.[56]
 - Vinblastine.
 - Vincristine.
- Platinum.
 - Carboplatin.
 - Cisplatin.
- Other.
 - Gemcitabine.[57]
 - Mitomycin C.

Combination regimens that have shown activity in metastatic breast cancer:

- CA: cyclophosphamide and doxorubicin.[58]
- Docetaxel and doxorubicin.[59]
- CAF: cyclophosphamide, doxorubicin, 5-fluorouracil.[60]
- CMF: cyclophosphamide, methotrexate, 5-fluorouracil.[61]
- Doxorubicin and paclitaxel [62,63]
- Docetaxel and capecitabine [64]
- Vinorelbine and epirubicin.[65]

EXHIBIT A